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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,377	12/18/2001	Michael Rosario DeFelippis	X-13134	1135

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EXAMINER
TELLER, ROY R

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,377	DEFELIPPIS ET AL.	
	Examin r	Art Unit	
	Roy Teller	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to Paper No: 4, received 12/18/01, in which applicant amended claims 4, 6, 20, and 24-26.

Claims 1-27 are pending.

Information Disclosure Statement

The information disclosure statement filed 5/29/02 (Paper No: 5) is acknowledged. A signed copy is attached hereto.

Specification

The use of the trademark "ULTRALENTE" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 contains the trademark/ trade name "ULTRALENTE". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/ trade name is used to identify/ describe and, accordingly, the identification/ description is indefinite.

Claim 1 recites "uni-modal". This is in vague and indefinite because uni-modal is not defined in the specification and no definition of the term is found in the Merriam-Webster's Collegiate Dictionary. It is thus unclear if the term is intended as a limitation in the claim.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under 35 USC 112, second paragraph for reasons set forth above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 7, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for insulin, does not reasonably provide enablement for an insulin analog, a derivatized insulin, or a derivatized insulin analog. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the

prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention:

The claimed invention is drawn to crystals comprising about 0.3 to about 2.0 mole insulin, an insulin analog, a derivatized insulin , or a derivatized insulin analog, and a divalent metal cation, to processes for preparing such crystals, and to methods of treating diabetes or hyperglycemia comprising administering the crystals via the pulmonary route to a patient in need, to control blood glucose. Crystals having a volume mean spherical equivalent diameter of 1-5 microns are obtained.

The state of the prior art and the predictability or lack thereof in the art: Hoffmann (USPN 5,534,488) teaches an insulin formulation comprising a suspension of Ultralente crystals and a total formulation zinc concentration of between about 0.5 mg. to about 20 mg. per 100 units of insulin (see abstract). Hoffmann discloses a method of treatment that is administered one time per day. The art does not teach formulations comprising an insulin analog, a derivatized insulin , or a derivatized insulin analog as claimed in the invention.

The amount of direction or guidance present and the presence or absence of working examples: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991).

While the instant specification provides guidance as to how to make and administer crystals

comprising insulin, there is no guidance directed to amking crystals comprising insulin analogs or derivatized insulin for administeration *in vivo* as a treatment for diabetes or hyperglycemia. There are no working examples directed to making crystals comprising insulin analogs or derivatized insulin. There are no working examples directed to treating diabetes or hyperglycemia with crystals compricsing insulin analogs or derivatized insulin.

The breadth of the claims and the quantity of experimentation needed:

Because neither the art nor the specification provides guidance as to how to prepare and administer insulin analogs, derivatized insulin or derivatized insulin analogs as therapeutics for treating diabetes and hyperglycemia it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffmann (USPN 5,534,488) in view of Schlichtkrull (USPN 2,819,999).

The claimed invention is drawn to crystals comprising about 0.3 to about 2.0 mole insulin, an insulin analog, a derivatized insulin , or a derivatized insulin analog, and a divalent metal cation, to processes for preparing such crystals, and to methods of treating diabetes or hyperglycemia comprising administering the crystals via the pulmonary route to a patient in need, to control blood glucose. Crystals having a volume mean spherical equivalent diameter of 1-5 microns are obtained.

Hoffmann teaches an insulin formulation comprising a suspension of Ultralente crystals and a total formulation zinc concentration of between about 0.5 mg. to about 20 mg. per 100 units of insulin (see abstract). Although Hoffmann does not teach about 0.3 to about 2.0 mole insulin, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have optimized. Hoffmann discloses a method of treatment that is administered one time per day (see column 12, claim 19). Hoffmann does not teach a crystal size.

Schlichtkrull teaches a process for crystallization of insulin, with the crystals ranging in size from 1 micron to 7 microns (see column 3, line 26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added the crystallization of insulin process of Schlichtkrull to the insulin formulation of Hoffmann, because Hoffmann used previously prepared suspensions of Ultralente insulin crystals (see column 4, line 43).

Claims 6-13, and 15-19 are rejected under 35 USC 103(a) as being unpatentable over Hoffmann in view of Schlichtkrull, as applied to claim 1 above, and further in view of DeFelippis (USPN 5,952,297).

The claimed invention is as described above, wherein the crystals are prepared by preparing a crystallization solution comprising insulin, an insulin analog, a derivatized insulin or a derivatized insulin analog, a buffer, a salt and a divalent cation; combining the crystallization solution with a nucleating seed suspension; and allowing time for the seeded crystallization solution to generate crystals.

DeFelippis teaches a seed suspension of human insulin (see column 6, example 1, lines 22-26). DeFelippis discloses sodium chloride, a physiologically acceptable buffer, a zinc ion, and a physiologically acceptable preservative (see column 9, claim 1). DeFelippis teaches that seed crystals are added to the solution to produce a more uniform size distribution of crystalline material and to accelerate the crystallization (see column 3, lines 41-43). DeFelippis discloses crystals precipate in about 6 to 72 hours (see column 3, lines 35-36).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have added the seed suspension of DeFelippis with the insulin formulation of Hoffmann, because Hoffmann used previously prepared suspensions of Ultralente insulin crystals (see column 4, line 43).

Conclusion

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy Teller whose telephone number is (703) 305-4243. The examiner can normally be reached on Monday-Friday from 5:30 am to 2:00 am.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (703) 306-3220. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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